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(54) Stable compositions for parenteral administration

(57) This invention relates to certain stable microsphere compositions containing a fat, a wax or a mixture thereof; and an active ingredient selected from LL-F28249α-λ, compounds, 23-oxo or 23-imino derivatives of LL-F28249α-λ compounds, milbemycin compounds and avermectin compounds. The invention also relates to a method for introducing and maintaining levels of the active compound in the blood of warm-blooded animals for extended periods of time and for the prevention or treatment of infections and infestations caused by helminths, nematodes, acarids and endo- and ectoparasitic arthropods in warm-blooded animals by the parenteral administration of compositions of the invention.

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Description

BACKGROUND OF THE INVENTION

[0001] Helminthiasis is a widespread disease found in many animals and is responsible for significant economic losses throughout the world. Among the helminths most frequently encountered are the group of worms referred to as nematodes. The nematodes are found in the intestinal tract, heart, lungs, blood vessels and other body tissues of animals and are a primary cause of anemia, weight loss and malnutrition in the infected animals. They do serious damage to the walls and tissue of the organs in which they reside and, if left untreated, may result in death to the infected animals.

[0002] The nematodes most commonly found to be the infecting agents of ruminants include Haemonchus and Ostertagia generally found in the abomasum; Cooperia, Trichostrongylus and Nematodirus generally found in the intestinal tract, and Dictyocaulus found in the lungs. In non-ruminant animals important nematodes include Toxocara and Ancylostoma in the intestine and Dirofilaria in the heart of dogs; Ascaris in the intestine of swine; Ascaridia and Heterakis in the intestine of poultry; and large and small strongyles in equines. Treatment of animals to prevent infestation thereof by the above nematodes or to reduce or control the proliferation of these infecting agents in animals is thus an important goal.

[0003] Macromolecules such as LL-F28249α-λ compounds, 23-oxo and 23-imino derivatives of LL-F28249α-λ compounds, milbemycin compounds and avermectin compounds are useful for the prevention and treatment of infections and infestations caused by helminths, nematodes, acarids and endo- and ectoparasitic arthropods when parenterally administered to warm-blooded animals. Parenteral compositions are sterilized prior to administration to an animal. Gamma radiation is an effective sterilization process for eliminating microbial contaminants. However, certain macromolecules such as LL-F28249α-λ compounds, 23-oxo and 23-imino derivatives of LL-F28249α-λ compounds, milbemycin compounds and avermectin compounds degrade and lose much of their biological activity when irradiated. This destructive and degradative response to gamma radiation precludes the use of gamma radiation as a means to sterilize certain macromolecule-containing compositions.

[0004] Formulations for parenteral administration to warm-blooded animals containing such macromolecules have been made using antioxidants to protect the macromolecules from degradation during irradiation, for example, according to Australian Patent Number 651229 and European Patent Number 525307.

[0005] It is desirable to have formulations for parenteral administration to warm-blooded animals that will release the active macromolecule slowly over a period of time to maintain a desirable and effective level of the drug in the bloodstream of a warm-blooded animal. AU 651229 and EP 525307 teach formulations that include both a relatively hard fat and/or wax and an oil, semi-soft fat and/or fatty acid derivative which is soluble in the hard fat/wax and aids in a physical transformation of the hard fat/wax.

SUMMARY OF THE INVENTION

[0006] The present invention relates to stable microsphere compositions which can be irradiation sterilized for parenteral administration. The compositions comprise or consist essentially of, on a weight basis, about 50% to 99% by weight of a fat, a wax or a mixture thereof having a melting point above about 40ºC, about 1% to 50% of an LL-F28249α-λ compound, a 23-oxo or 23-imino derivative of an LL-F28249α-λ compound, a milbemycin compound or an avermectin compound, and about 0-10% of an anti-oxidant.

[0007] Preferably the microsphere compositions of this invention do not contain an oil, semi-soft fat and/or fatty acid derivative as used in EP 525307.

Suprisingly, it has been found that the microsphere compositions of the invention can be sterilized by gamma radiation without degradation of its biological activity. Also unexpectedly, the microsphere compositions can achieve an effective sustained release effect of the water-insoluble, complex macrolides.

The invention also provides a method for introducing and maintaining blood levels of an LL-F28249α-λ compound, a 23-oxo or 23-imino derivative of an LL-F28249α-λ compound, a milbemycin compound or an avermectin compound in warm-blooded animals for an extended period of time; and a method for the prevention or treatment of infections and infestations caused by helminths, nematodes, acarids and endo- and ectoparasitic arthropods in warm-blooded animals.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008]

Fig. 1 illustrates and compares the release kinetics of a formulation of the invention and a formulation not within

the scope of the invention.

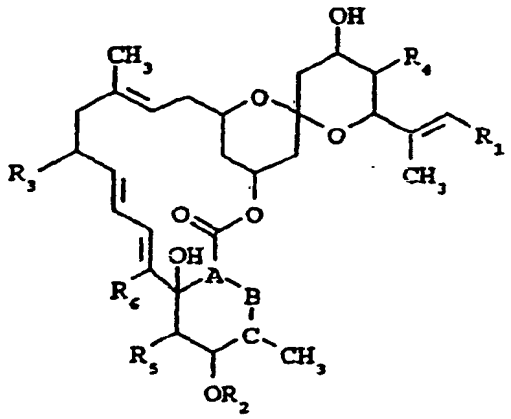
DETAILED DESCRIPTION OF THE INVENTION

[0009] One important aspect of the present invention is stable, slow release microsphere compositions which comprise an LL-F28249α-λ compound, a 23-oxo or 23-imino derivative of an LL-F28249α-λ compound, a milbemycin compound or an avermectin compound, dissolved in a fat, a wax or a mixture thereof having a melting point above about 40ºC, and preferably above about 50ºC. These microsphere compositions may be sterilized by gamma radiation without significant degradation. The microsphere compositions of this invention are suitable for parenteral administration by dispersion in a pharmaceutically and pharmacologically acceptable liquid vehicle.

[0010] Preferred stable microsphere compositions of the invention comprise on a weight basis about 75% to 95% by weight of a fat, a wax or a mixture thereof. Preferably they contain about 5% to 25% of an active ingredient selected from the group consisting of an LL-F28249α-λ compound, a 23-oxo cr 23-imino derivative of an LL-F28249α-λ compound, a milbemycin compound or an avermectin compound. Preferably they contain about 0.01-1% of an antioxidant.

[0011] The compounds designated LL-F28249α-λ are (collectively) isolates from the fermentation broth of the microorganism *Streptomyces cyaneogriseus* subspecies *noncyanoyenus*, deposited in the NRRL under deposit accession No. 15773. The method for preparation of LL-F28249α is disclosed in United States Patent No. 5,106,994 and its continuation, United States Patent No. 5,169,956, which are incorporated herein by reference thereto.

[0012] The LL-F28249α-λ compounds are represented by the following structural formula:



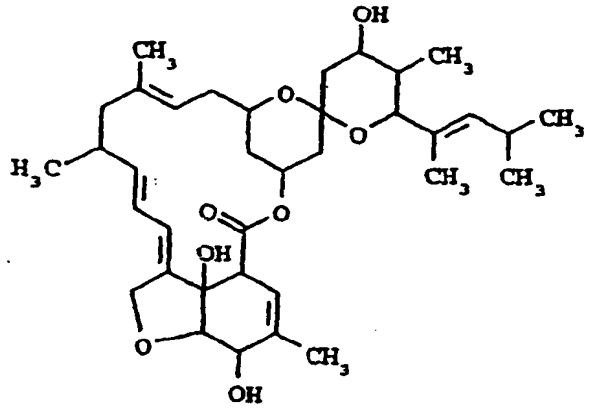
LL-F28249α-λ

Table I, below, identifies the meanings of the variables A, B, C, and R_{1-6} for each compound of this formula.

TABLE I

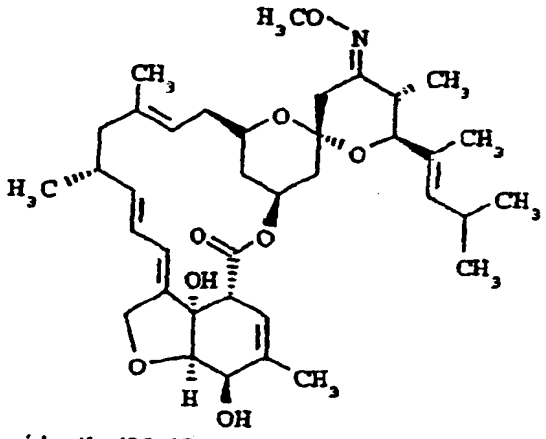
LL-F28249	R_1	R_2	R_3	R_4	R_5	R_6	R_5+R_6	A-B	B-C
alpha	$CH(CH_3)_2$	H	CH_3	CH_3			-O-CH_2-	CH-CH	CH=C
beta	CH_3	H	CH_3	CH_3			-O-CH_2-	CH-CH	CH=C
gamma	CH_3	CH_3	CH_3	CH_3			-O-CH_2-	CH-CH	CH=C
delta	CH_3	CH_3	CH_3	CH_3	OH	CH_2OH		CH-CH	CH=C
epsilon	$CH(CH_3)_2$	H	H	CH_3			-O-CH_2-	CH-CH	CH=C
zeta	CH_2CH_3	H	CH_3	CH_3			-O-CH_2-	CH-CH	CH=C
eta	$CH(CH_3)_2$	H	CH_3	CH_3			-O-CH_2-	C=CH	CH-CH
theta	$CH(CH_3)_2$	H	CH_3	CH_2CH_3			-O-CH_2-	CH-CH	CH=C
iota	$CH(CH_3)_2$	H	CH_2CH_3	CH_3			-O-CH_2-	CH-CH	CH=C
kappa	CH_3	CH_3	CH_3	CH_3	H	CH_3		CH-CH	CH=C
lambda	$CH(CH_3)_2$	CH_3	CH_3	CH_3			-O-CH_2-	CH-CH	CH=C

[0013] The 23-oxo and 23-imino derivatives of LL-F28249α-λ compounds, useful in the present invention, are disclosed in U.S. Patent Number 4,916,154, which is herein incorporated by reference. Preferred compounds for use in this invention include:



LL-F28249α

and



moxidectin (23-(O-methyloxime)-LL-F28249α).

[0014] Waxes and fats which are suitable in the compositions of this invention generally have melting points higher than 40°C, preferably higher than 50°C.

[0015] The term "wax" as used herein is defined as set forth in Hawley's *The Condensed Chemical Dictionary*, Eleventh Edition, as a low-melting organic mixture or compound of high molecular weight, solid at room temperature and generally similar in composition to fats and oils except that it contairs no glycerides. Some are hydrocarbons; others are esters of fatty acids and alcohols. These compounds include saturated or unsaturated long chain C_{10}-C_{24} fatty adds, alcohols, esters, salts, ethers or mixtures thereof. They are classed among the lipids. Waxes are thermoplastic, but since they are not high polymers, they are not considered in the family of plastics. Common properties of these waxes include water repellency; smooth texture; nontoxicity; and freedom from objectionable odor and color. They are combustible and have good dielectric properties. They are soluble in most organic solvents and are insoluble in water. The major types are as follows:

I. Natural

1. Animal (beeswax, lanolin, shellac wax, Chinese insect wax)
2. Vegetable (camauba, candelilla, bayberry, sugar cane)

3. Mineral (a) Fossil or earth waxes (ozocerite, ceresin, montan) (b) petroleum waxes (paraffin, microcrystalline) (slack or scale wax)

II. Synthetic

1. Ethylenic polymers and polyol ether-esters ("Carbowax")
2. Chlorinated naphthalenes ("Halowax")
3. Hydrocarbon type via Fischer-Tropsch synthesis

[0016] The term "fat" as used herein is defined as set forth in Hawley's *The Condensed Chemical Dictionary,* Eleventh Edition, as a glyceryl ester of higher fatty acids such as stearic and palmitic. Such esters and their mixtures are solids at room temperatures and exhibit crystalline structure. Lard and tallow are examples. The term "fat" usually refers to triglycerides specifically, whereas "lipid" is all-inclusive.

[0017] The fat is preferably composed of triglyceryl esters of long chain C_{12}-C_{22} fatty acids, such as stearates, palmitates, laurates, myristates, arachidates and behenates, and mixtures thereof; those having melting points greater than 50°C are most preferred. Glyceryl tristearate is a most preferred fat in the practice of this invention. Additionally, lipophilic salts of fatty acids such as magnesium stearate and the like are also suitable.

[0018] An anti-oxidant suitable in the practice of this invention includes any of the antioxidants known in the art as suitable for stabilizing the macromcleeules of this invention. One preferred anti-oxidant is BHT (butylated hydroxytoluene).

[0019] The microsphere compositions of the invention may be sterilized with gamma radiation and maintain shelf life without significant loss of biological activity.

[0020] The stable microspheres of the invention are dispersed in a pharmaceutically and pharmacologically acceptable aqueous solution to obtain a slow release composition for parenteral administration.

[0021] Excipients such as surfactants, salts, buffers or mixtures thereof may be included in the vehicle of the invention. The amounts of said excipients suitable for use in the invention range from about 0.1% to 20% on a weight basis. Preferably, a cellulose derivative such as hydroxypropylmethylcellulose comprises about 1-5% by weight and an inorganic salt, e.g., NaCl, comprises about 0.1-2% by weight of the vehicle.

[0022] Blood levels of the LL-F28249α-λ compounds, 23-oxo and 23-imino derivatives of LL-F28249α-λ compounds, milbemycin compounds and avermectin compounds may be obtained and maintained for extended periods of time by injecting animals with the compositions of the invention in a suitable vehicle. Unexpectedly, the water-insoluble macrolide antibiotics can be effectively delivered from the microsphere formulation for a sustained release effect.

[0023] Maintained blood levels of the active compounds are associated with the protection or treatment of warm-blooded animals against infections and infestation by helminths, nematodes, acarids and endo- and ectoparasitic arthropods. Maintaining the blood levels is an indication of the slow release of the active ingredient. The invention indudes the use of the compositions herein to introduce and maintain levels of LL-F28249α-λ compounds, 23-oxo and 23-imino derivatives of LL-F28249α-λ compounds, milbemycin compounds and avermectin compounds in the blood stream of animals.

[0024] When parenterally administered, the compositions of this invention are highly effective for protecting or treating warm-blooded animals such as dogs, cats, cattle, sheep, horses, swine, goats, poultry and the like against infection and infestation by helminths, nematodes, acarids and endo- and ectoparasitic arthropods, including arthropod endoparasitic infestations such as cattle grub and ecto-parasitic infestations such as psoroptic mange.

[0025] The microspheres of the invention may be prepared by dissolving the active ingredient, and optionally an antioxidant, in a molten fat, wax or mixture thereof and then forming microspheres of the resulting hot solution by any of the variety of techniques known in the art, such atomizing the solution. Alternatively, the solution of active ingredient and fat, waxes and mixtures thereof may be cooled to give a solid which may then be processed by procedures such as milling, grinding and the like. The microspheres, preferably fat microspheres, may be up to 1,000 microns in diameter, with a weight average size range of about 25 microns to 300 microns being preferred for parenteral administration. Preferably, the microspheres have a diameter in the approximate range of 90-180 microns.

[0026] In order to facilitate a further understanding of the invention, the following examples are presented primarily for the purpose of illustrating more specific details thereof. The invention is not to be deemed limited thereby except as defined in the claims.

EXAMPLE 1: Preparation of 10% Moxidectin Microspheres

[0027] Glyceryl tristearate (GTS), 888.9 g., is melted in a vessel and brought to approximately 100-110°C with stirring. Moxidectin powder, 111.1 g., 90% purity and containing 0.3 - 0.4% BHT, is added to the molten GTS and stirred at 100-145°C until the powder dissolves. The hot solution is transparent and slightly yellow. This solution is transferred

to an atomizing apparatus having a two-fluid nozzle or wheel atomizer, which has been preheated to about 90-110°C and set up in a spray chamber. The solution is spray atomized and microspheres of about 9C-180 microns in diameter are recovered using sieves. The microspheres are filled into containers and the containers are then purged with inert gas, sealed, and gamma-irradiated to achieve sterilization.

EXAMPLE 2: Preparation of 10% Moxidectin Microspheres

[0028] Glyceryl tristearate (GTS), 8.8 g., is melted in a vessel and brought to approximately 100-110°C with stirring. Moxidectin powder, 1.0 g., 98.9% purity and BHT, 0.002 g, is added to the molten GTS and stirred at 100-145°C until the powder dissolves. The hot solution is transparent and slightly yellow. This solution is atomized, stored and sterilized according to the procedure of Example 1.

EXAMPLE 3: Preparation of Moxidectin Microspheres Vehicle

[0029] A vehicle containing the following ingredients is prepared as described below:

	%w/v	grams
NaCl	0.9	90
HPMC*	2.5	250
methylparaben	0.18	18
propylparaben	0.02	2
Water for injection, USP	q.s.	q.s.
Total =	100%	10 liters

*Hydroxypropylmethylcellulose (Dow, Methocel E50, or equivalent)

[0030] Approximately 50% of the water for injection is charged to a vessel and heated to about 70-80°C, and the NaCl, methylparaben and propylparaben are each added and stirred until dissolved. The HPMC is added slowly with stirring to achieve dispersion. The heat is removed and cold water for injection added to bring the volume to 10 liters. The formulation is chilled to about 5-10°C to achieve complete solubilization of the HPMC. The pH is adjusted to 4.5-5.5 by adding HCl and the solution is filtered to achieve sterilization. The vehicle solution is stored in sterile containers.

EXAMPLE 4: Making and Using the Final Formulation

[0031] At the point of use, the vehicle made in Example 3 is added to the microspheres made in Example 1 and the container is shaken to disperse the microspheres in the vehicle. The formulation is then drawn into a syringe in a dose volume specified for the body weight of the dog to be treated and injected subcutaneously.

[0032] When a dosage of 3.5 mg of the final formulation per kg body weight is administered to dogs, the following data are collected.

Dosage: 3.5 mg/kg, 10% moxidectin in microspheres (90-180 microns). N = 4 dogs.	
Days after dosing	Average moxidectin, ppb, in blood
1	10.8
2	18.5
4	28.3
7	30.8
10	26.5
14	32.0
21	24.6
28	22.7
35	23.2
42	24.0
49	21.5
56	16.0

(continued)

Dosage: 3.5 mg/kg, 10% moxidectin in microspheres (90-180 microns). N = 4 dogs.	
Days after dosing	Average moxidectin, ppb, in blood
63	15.3
70	16.8
77	13.8
84	12.0
98	8.6
112	9.4
126	10.4
140	9.0
147	6.6
161	7.0
175	7.0

[0033] These data indicate a release half-life of 73 days. These data are shown graphically in Fig. 1.

COMPARATIVE EXAMPLE

[0034] A formulation made according to AU 651229 and EP 525307 was administered parenterally to dogs at a dosage of 1.7 mg/kg body weight These microspheres comprised 10% moxidectin in 9:1 glyceryl tristearate/Miglyol 812 (a triglyceride oil). The results are presented in the table below and illustrated in Fig. 1.

Dosage: 1.7 mg/kg, 10% moxidectin in microspheres (90-180 microns). N = 4 dogs.	
Days after dosing	Average moxidectin, ppb, in blood
1	38.5
3	80.3
8	100.0
15	50.0
22	28.8
29	21.3
35	14.0
42	9.5
49	6.5
56	5.0

[0035] These data indicate a release half-life of 12 days. It is apparent from the data in this Comparative Example and in Example 3 that the formulation of the present invention releases the active ingredient more gradually than does the comparative formulation. The formulation of this invention thus provides a level of active ingredient in the blood-stream that is more constant and long-lasting.

Claims

1. A microsphere composition comprising from about 1% to about 50% by weight of a compound selected from the group consisting of an LL-F28249α-λ, a 23-oxo or 23-imino derivatives of an LL-F28249α-λ, a milbemycin and an avermectin; from about 50% to about 99% by weight of a fat, wax or mixture thereof having a melting point higher than about 40C, and 0-10% of one or more anti-oxidant compounds.

2. A microsphere composition comprising from about 1% to about 50% by weight of a compound selected from the group consisting of an LL-F28249α-λ, a 23-oxo or 23-imino derivatives of an LL-F28249α-λ, a milbemycin and an avermectin; from about 50% to about 99% by weight of a fat, wax or mixture thereof having a melting point higher than about 40C, and 0-10% of one or more anti-oxidant compounds, further **characterized in that** the composition

does not contain an oil, semi-soft fat and/or fatty acid derivative.

3. A microsphere composition according to Claim 1 or Claim 2 wherein said compound comprises from about 1% to about 25% by weight of the composition.

4. A microsphere composition according to any one of Claims 1 to 3 wherein said compound is moxidectin.

5. A microsphere composition according to any one of Claims 1 to 4 in which the fat, wax or mixture thereof has a melting point higher than about 50C,

6. A microsphere composition according to any one of Claims 1 to 5 wherein said fat, wax or mixture thereof comprises from about 75% to about 95% by weight of the composition.

7. A microsphere composition according to any one of Claims 1 to 6 wherein said fat, wax or mixture thereof comprises a fatty acid ester.

8. A microsphere composition according to Claim 7 wherein said fatty acid ester is a triglyceryl ester of fatty acids which fatty acids each contain 12-22 carbon atoms.

9. A microsphere composition according to Claim 7 wherein said fatty acid ester is glyceryl tristearate.

10. A microsphere composition according to any one of Claims 1 to 9 wherein said anti-oxidant comprises from about 0.01% to about 1% by weight of the composition.

11. A microsphere composition according to Claim 1 comprising moxidectin in an amount from about 9-12% by weight, glyceryl tristearate in an amount from 87-89% by weight and the remainder is anti-oxidant.

12. A microsphere composition according to any one of Claims 1 to 11 wherein said anti-oxidant comprises butylated hydroxytoluene.

13. A microsphere composition according to any one of Claims 1 to 12 which has a diameter up to about 1000 microns.

14. A microsphere composition according to any one of Claims 1 to 13 which has a diameter in the range about 90 to about 180 microns.

15. A pharmaceutical composition suitable for injection into a warm-blooded animal comprising a microsphere composition according to any one of Claims 1 to 14 and a pharmaceutically acceptable aqueous vehicle.

16. A pharmaceutical composition according to Claim 15 wherein said aqueous vehicle comprises from about 1 - about 5% by weight of hydroxypropylmethylcellulose.

17. A composition for parenteral administration to warm-blooded animals comprising:

(a) microspheres consisting essentially of about 1-25% by weight of a compound selected from an LL-F28249α-λ, a 23-oxo or 23-imino derivative of an LL-F28249α-λ, a milbemycin and an avermectin; a triglyceryl ester of fatty acids each having 12-22 carbon atoms, said ester having a melting point higher than about 50C and capable of dissolving said compound when in a molten state, and 0-10% of one or more anti-oxidant compounds; and,

(b) a pharmaceutically acceptable aqueous vehicle.

18. A composition according to Claim 17 wherein said triglyceryl ester of fatty acids comprises glyceryl tristearate.

19. Use of a composition according to any one of Claims 1 to 18 in the preparation of a medicament for protecting or treating warm-blooded animals against infection or infestation by helminths, nematodes, acarids or endo- or ectoparasitic arthropods in a warm-blooded animal.

20. Use of a composition according to any one of Claims 1 to 18 in the preparation of a medicament for introducing

and maintaining blood levels of a compound selected from an LL-F28249α-λ, a 23-oxo or 23-imino derivative of an LL-F28249α-λ, a milbemycin and an avermectin in a warm-blooded animal.

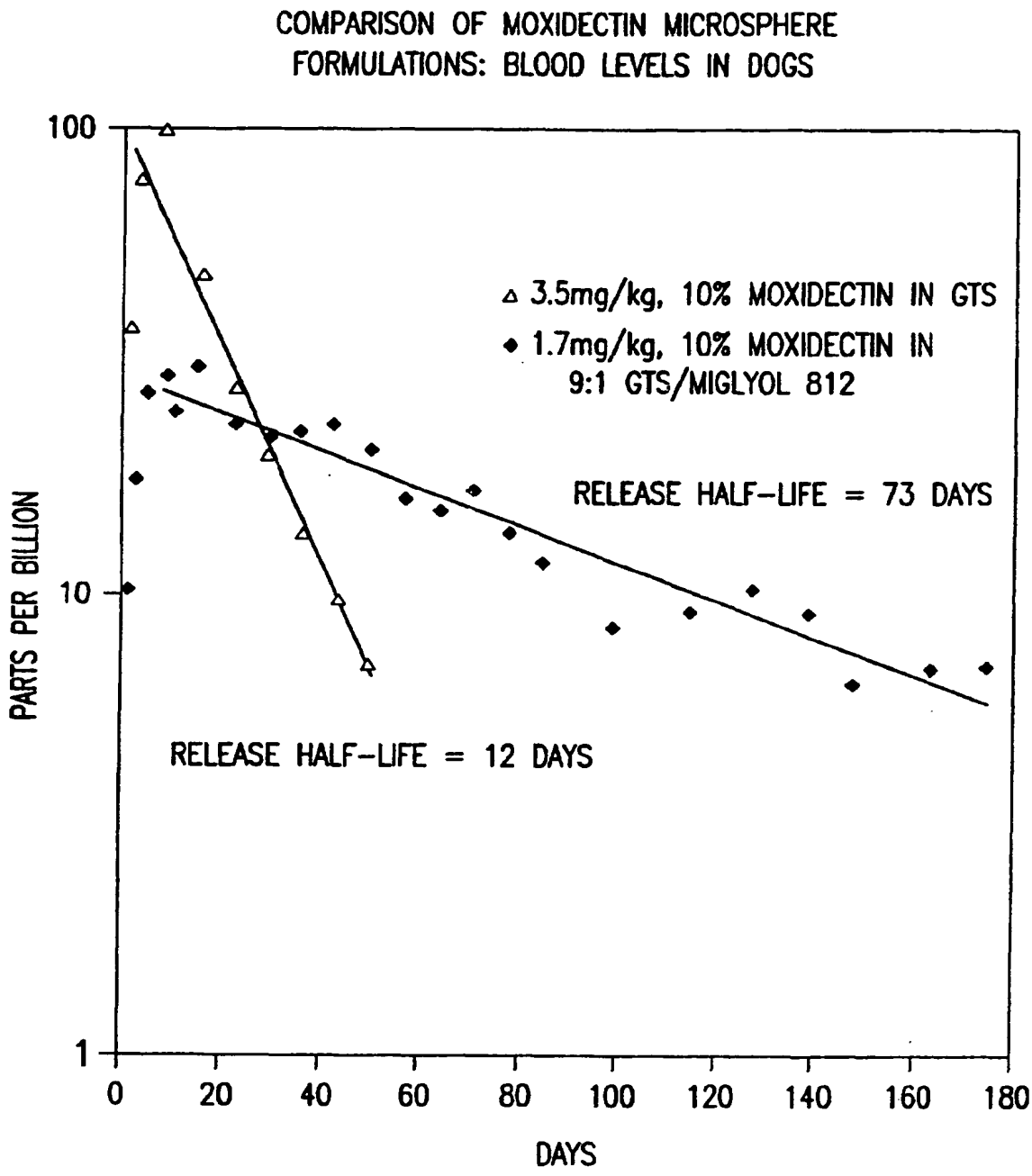


FIG.1

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(54) Stable compositions for parenteral administration

(57) This invention relates to certain stable microsphere compositions containing a fat, a wax or a mixture thereof; and an active ingredient selected from LL-F28249α-λ, compounds, 23-oxo or 23-imino derivatives of LL-F28249α-λ compounds, milbemycin compounds and avermectin compounds. The invention also relates to a method for introducing and maintaining levels of the active compound in the blood of warm-blooded animals for extended periods of time and for the prevention or treatment of infections and infestations caused by helminths, nematodes, acarids and endo- and ectoparasitic arthropods in warm-blooded animals by the parenteral administration of compositions of the invention.

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 01 30 8284

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X,D	EP 0 525 307 A (AMERICAN CYANAMID) 3 February 1993 (1993-02-03) * claims * * examples *	1-20	A61K9/16 A61K31/365
A	GB 2 310 801 A (MERCK) 10 September 1997 (1997-09-10) * claims * * examples *	1-20	
A	US 5 733 566 A (D.H.LEWIS) 31 March 1998 (1998-03-31) * claims * * examples *	1-20	
A	EP 0 448 930 A (AMERICAN CYANAMID) 2 October 1991 (1991-10-02) * claims * * examples *	1-20	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	12 December 2002	Scarponi, U

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 30 8284

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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12-12-2002

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 525307	A	03-02-1993	AT	134873 T	15-03-1996
			AU	651229 B2	14-07-1994
			AU	2047292 A	28-01-1993
			BR	9202771 A	23-03-1993
			CA	2074348 A1	24-01-1993
			CN	1068735 A ,B	10-02-1993
			DE	69208765 D1	11-04-1996
			DE	69208765 T2	26-09-1996
			DK	525307 T3	01-04-1996
			EP	0525307 A1	03-02-1993
			ES	2086022 T3	16-06-1996
			GR	3019234 T3	30-06-1996
			HK	1000005 A1	03-10-1997
			HU	62454 A2	28-05-1993
			IE	922373 A1	27-01-1993
			IL	102567 A	31-10-1996
			JP	5194211 A	03-08-1993
			KR	235550 B1	15-12-1999
			MX	9204135 A1	01-01-1993
			NZ	243619 A	22-12-1994
			US	6340671 B1	22-01-2002
			ZA	9205522 A	28-04-1993
GB 2310801	A	10-09-1997	NONE		
US 5733566	A	31-03-1998	US	5419910 A	30-05-1995
			US	5288496 A	22-02-1994
			US	5643595 A	01-07-1997
			US	5686092 A	11-11-1997
			US	5427796 A	27-06-1995
			US	5401507 A	28-03-1995
EP 448930	A	02-10-1991	US	5213810 A	25-05-1993
			AT	106240 T	15-06-1994
			AU	641994 B2	07-10-1993
			AU	7397291 A	03-10-1991
			BG	60850 B1	31-05-1996
			CA	2039491 A1	01-10-1991
			CN	1055293 A ,B	16-10-1991
			CZ	283053 B6	17-12-1997
			DE	69102176 D1	07-07-1994
			DE	69102176 T2	05-01-1995
			DK	448930 T3	20-06-1994
			EP	0448930 A1	02-10-1991
			ES	2054380 T3	01-08-1994
			FI	911531 A	01-10-1991

EPO FORM P0469

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 30 8284

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

12-12-2002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 448930 A		HK 1000004 A1	03-10-1997
		HU 59834 A2	28-07-1992
		IE 911041 A1	09-10-1991
		IL 97145 A	18-06-1996
		JP 2966564 B2	25-10-1999
		JP 4221319 A	11-08-1992
		KR 159778 B1	01-12-1998
		MX 172602 B	03-01-1993
		NO 911228 A	01-10-1991
		NZ 237509 A	28-04-1993
		PL 289657 A1	13-01-1992
		PT 97160 A ,B	29-11-1991
		RO 106191 B1	31-03-1993
		SK 279461 B6	04-11-1998
		RU 2011377 C1	30-04-1994
		ZA 9102398 A	29-01-1992

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82